ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Autoimmune Liver Diseases: A Multicentre Cross-Sectional Study by the Italian Association for the Study of Liver Disease

Annarosa Floreani[1], Piero Luigi Almasio[2]*, Tommaso Stroffolini[3], Alessandra Buja[4], Silvia Ferri[5], Marco Lenzi[5] and the AISF Autoimmune Liver Disease Group[6]

[1]Department of Surgery, Oncology and Gastroenterology, University of Padua, Italy

[2]Gastroenterology and Hepatology Unit, Dipartimento Biomedico di Medicina Interna e Specialistica (Di.Bi.M.I.S.), University of Palermo, Italy

[3]Tropical Diseases Unit, Policlinico Umberto I, Rome, Italy

[4]Laboratory of Public Health and Population Studies, Department of Molecular Medicine, University of Padua, Italy

[5]Department of Medical and Surgical Sciences, University of Bologna, Italy

[6]Maria Rendina, Azienda Ospedaliero-Universitaria Consorziale, Policlinico di Bari; Martina Felder, Ospedale Bolzano; Guido Colloredo, Policlinico S. Pietro, Ponte S. Pietro, Bergamo; Pierluigi Frugiuele, Azienda Ospedaliera, Cosenza; Pietro Andreone, Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna; Ruggiero Francavilla, Giancarlo Labbadia Ospedale Civile di Bisceglie, Bitonto; Carmen Vandelli, Az. Ospedaliero-Universitaria, Modena; Erberto Ferretti, Presidio Intermedio Napoli Est, Napoli; Giorgio Soardo, Azienda Ospedale-Università S. Maria della Misericordia, Udine; Francesco Salerno, Policlinico IRCCS San Donato Milanese, Milan; Vincenzo Portelli, Ospedale S. Antonio, Erice, Trapani, Italy

***Corresponding Author**: Piero Luigi Almasio, Gastroenterology and Hepatology Section, Dipartimento Biomedico di Medicina Interna e Specialistica, Università di Palermo, Piazza delle Cliniche, 2 90127 Palermo, Italy.

Received: November 10, 2016**; Published:** November 25, 2016

Abstract

Background and Aim: Epidemiological data on autoimmune liver diseases in Italy are lacking. We aimed to characterise demographic and clinical features of autoimmune liver diseases in Italy.

Methods: A nationwide multicentre survey of prevalent and incident cases of liver disease was performed from January to December 2010. Fifteen Italian centres adhered to the study, and 562 completed questionnaires were collected.

Results: Among enrolled cases, 453 (80.6%) were prevalent and 109 (19.4%) were incident cases. Mean age was 54.1 ± 14.9 years (range 17-90); 113 were males (20.1%) and 449 (79.9%) females; 254 cases fulfilled the diagnosis of autoimmune hepatitis (45.2%), 234 of primary biliary cholangitis (41.6%), and 41 of primary sclerosing cholangitis (7.3%); 33 subjects (5.9%) were diagnosed as overlap syndrome. The predominant type of autoimmune hepatitis was type I (93.7%), and half of them exhibited an "acute" onset. The different types of liver disease significantly differed in terms of age, gender and their associations with other extra hepatic autoimmune diseases.

Conclusion: In conclusion, autoimmune liver diseases in Italy are predominantly diagnosed in the female gender and the clinical onset in approximately 50% of cases resembles acute hepatitis. Overlap syndromes are very rare and affect just a small proportion of patients.

Keywords: *Autoimmune Liver Diseases; Epidemiology; Acute Hepatitis; Autoantibodies*

Introduction

Autoimmune liver diseases include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) formerly called primary biliary cirrhosis, primary sclerosing cholangitis (PSC), and the overlap syndromes between AIH and PBC and between AIH and PSC. AIH is a

progressive inflammatory disorder characterised serologically by high levels of transaminases and immunoglobulin G and the presence of non-organ-specific autoantibodies, and histologically by interface hepatitis in the absence of any known aetiology [1]. The median age at diagnosis is 40 years in men and 50 years in women [2].

Prevalence and incidence data are still limited, but estimated prevalence ranging between 50 and 200 cases per million have been reported for Western Europe and North America with respect to the Caucasian population [3]. The most important nationwide published studies on AIH are reported in Table 1 [4-11]. The majority of the studies are multicentre and retrospective and were performed through the analysis of questionnaires or medical records. The sample size for the individual studies ranges between 25 and 1,721 subjects with a mean age of disease onset ranging from 50 to 68 years, with the exception of the Swedish study that also includes paediatric cases [5]. Only one study includes cases with "acute onset" [7]. The prevalence of cirrhosis at presentation ranges between 6.4 and 33%.

Author	Country	Period	Data Source	No. of cases	"Acute" onset	Associated auto immune conditions	Mean age at diagnosis (years)	Prevalence of cirrhosis at onset (%)
Boberg., *et al.* 1998 [4]	Norway	1986-1995	Medical record prospectively collected	25	N.A.	N.A.	68 (26-80)	28
Hurlburt., *et al.* 2002 [5]	Alaska	1983-2000	Medical record collection	42	17 (34.7%)	N.A.	52 (15-82)	N.A.
Werner., *et al.* 2008 [6]	Sweden	1990-2003	Medical record collection	473	N.A.	232 (49%)	43 (4.5-84)	33
Ngu., *et al.* 2010 [7]	New Zealand	Before 2008	Prospective and retrospective analysis	138	N.A.	N.A.	50	N.A.
Abe., *et al.* 2011 [8]	Japan	Before 2009	Questionnaire	1056	95 (10.9%)	284 (26.9%)	59.9 ± 14.7	6.4
Kim., *et al*. 2012 [9]	Korea	2005-2009	Questionnaire	343	N.A.	51.2%	52.8 ± 14.4	22.7
Gronbaek., *et al.* 2014 [10]	Denmark	1994-2012	Nationwide health care registry	1721	N.A.	N.A.	Incidence peak around 70 yrs	28.3
Van Gerven., *et al.* 2014 [11]	Nederland	1967-2011	Medical record retrospective analysis	1313	254/564 (45%)	335(26%)	48 (5-87) female 43 (6-87) male	12%

Table 1: *Nationwide studies addressing autoimmune hepatitis.*

PBC is a chronic cholestatic liver disease characterised by the presence of highly specific anti-mitochondrial antibodies (AMA) that predominantly affects females and eventually progresses to cirrhosis [12]. The reported rates of PBC prevalence range between 19 and 402 cases per million; the annual incidence of PBC is also highly variable, ranging from 0.33 to 5.8 per 100,000 persons/year [13].

Epidemiological data for both AIH and PBC are lacking in relation to Italy. A prevalence study undertaken in 79 Italian Hospitals in 2001, involving 9,997 patients, found that the prevalence of AIH was 0.8% and that of PBC 0.5% [14]. It should be stressed, however, that this survey addressed hospitalised cases only, and that both the presentation and natural history of both AIH and PBC have changed over the last 20 years: nowadays, most cases are diagnosed at an early stage of the disease when the patients are still asymptomatic. The consequence is that the management of AIH and PBC is mostly performed in outpatient clinics.

PSC is a chronic liver disease characterised by the chronic destruction of the bile ducts and progression to end-stage liver disease [15]. Its incidence varies geographically and is as high as 1-3 per 100,000 people per year in northern Europe; its prevalence is also variable, in some studies reported to be as high as 16.2 per 100,000 people [16-18]. In Italy, PSC is considered a rare disease, according to the definition that a rare disease affects no more than 5 individuals per 10,000.

The 1998 - 2000 Italian National Health Plan listed the "safeguarding of subjects affected by rare diseases" as one of its priorities and the creation of a National Network of rare diseases as one of its primary actions. Thus, the identification of rare diseases and their actual epidemiology would improve the activities of the National Network in the attempt to safeguard the equity principle of assistance for all citizens.

The aims of this cross-sectional study that involved several Italian centres under the auspices of the Italian Association for the Study of the Liver (AISF) were to describe the demographic and clinical features of autoimmune liver diseases in Italy in 2010, namely AIH, PBC, PSC and the AIH/PBC and AIH/PSC overlap syndromes.

Methods

From January 2010 to December 2011, all members of the AISF were invited to participate in a questionnaire-based investigation. Patients were considered eligible for inclusion if they were > 17 years and if they met the diagnostic criteria for AIH, PBC, PSC, or the AIH/PBC or AIH/PSC overlap syndromes. The diagnosis of AIH was made on clinical, immunological and histological grounds. Acute presentation was defined by the presence of recent onset (< 30 days) and symptoms (jaundice and/or fatigue and/or drowsiness) in conjunction with serum alanine transferase (ALT) levels higher than 10-fold the upper normal levels (UNL).

PBC was diagnosed on the basis on an AMA positivity titre greater than 1:40, abnormal alkaline phosphatase levels (at least 1.5 times the UNL), and/or compatible liver histology. Histological findings were classified according to Scheuer [19]. The diagnosis of AMA negative PBC was considered when the following criteria were met: AMA negativity, antinuclear antibodies (ANA) present at a titre of at least 1:160, abnormal liver function tests, diagnostic or compatible liver histology.

The diagnosis of PSC was based on the cholangiographic criteria obtained by endoscopic retrograde cholangiography (ERCP) or by nuclear magnetic resonance (NMR).

The diagnosis of AIH/PBC overlap syndrome was considered using the criteria described by Chazouillères., *et al* [20]. In brief, patients were considered to present AIH features if 2 or 3 of the following criteria were met: 1) ALT levels at least 5-fold higher than the UNL for the local laboratory; 2) serum IgG levels at least 2-fold higher than the UNL and/or positivity for smooth muscle autoantibodies (SMA); 3) liver biopsy showing moderate or severe periportal or periseptal lobular inflammation.

The diagnosis of AIH/PSC overlap syndrome was established when the following criteria were met: i) a total aggregate simplified score for AIH > 7 [21], defining AIH as "definite"; ii) ANA or SMA present at a titre of at least 1:40; and iii) liver histology with interface hepatitis, lymphocyte resetting, moderate or severe periportal or periseptal lobular inflammation.

Statistical Analyses

For each patient, the following variables were reported: age, sex, body mass index, of autoantibodies positivity, serum HBsAg, anti-HBc, HCV-RNA, liver histology, clinical presentation, association with another extra-hepatic autoimmune diseases and type of treatment.

The completed questionnaires were received by e-mail. Data were centrally recorded in an electronic data base and analysed at the end of the survey. To ensure anonymity, all personal data were blinded in the general database. For continuous variables, data were expressed as medians or means ± SD (standard deviation); normality was verified using the Shapiro-Wilk test. When normally distributed, mean differences between groups were compared by ANOVA. In cases where the assumption of normality was violated, data were analysed using the non-parametric Kruskal-Wallis test. For categorical variables, the absolute and relative frequencies were reported for each group. Categorical data were compared using the Pearson's chi-squared test. In the case that the expected cell frequencies were lower than 5, Fisher's exact test was applied. Analyses were performed using the STATA software. The level of significance was set at $p < 0.001$ to take into account multiple comparisons.

Results

Fifteen Italian centres adhered to the study, and 562 questionnaires were collected. The clinical characteristics are summarised in table 2. Of the 562 cases of autoimmune liver disease, 453 (80.6%) were prevalent and 109 (19.4%) were incident cases. The mean age was 54.1 ± 14.9 years (range 17 - 90); 113 were males (20.1%) and 449 (79.9%) females. 254 cases met the diagnostic criteria for of AIH (45.2%), 234 for PBC (41.6%), and 41 for PSC 87.3%); 28 subjects (5%) were diagnosed as having AIH/PBC overlap syndrome and 5 (0.9%) AIH/PSC overlap syndrome.

Variable	
Age (mean ± SD, range)	54.1 ± 14.9 (17-90)
Gender Male Female	113 (20.1%) 449 (79.9%)
Prevalent cases	453 (80.6%)
Diagnosis AIH PBC PSC AIH/PBC overlap AIH/PSC overlap	254 (45.2%) 234 (41.6%) 41 (7.3%) 28 (5.0%) 5 (0.9%)

Table 2: *General clinical characteristics of the patient population (n = 562 cases of autoimmune liver disease) at diagnosis.*

The comparison between AIH, PBC and PSC is shown in Table 3. The groups significantly differed in terms of age (patients with PSC were significantly younger than those with PBC or AIH, $p < 0.001$), gender (more females presented PBC or AIH than PSC, $p < 0.001$), association with other extra-hepatic autoimmune diseases (that were more frequently associated with PSC than with PBC or AIH, $p < 0.002$), and the clinical presentation as "acute hepatitis", defined by the presence of jaundice and clinical symptoms (which was as frequent as 49.6% in the AIH patient group, $p < 0.001$). Associated inflammatory bowel disease (ulcerative colitis or Crohn's disease) was present in 18/41 patients with PSC (46.5%).

Variable	PBC (n=234)	AIH (n=254)	PSC (n=41)	P
Age at diagnosis	52.7; 52.2 (±12.0)	48.1; 47.1 (±16.7)	30.0; 35.0 (±15.0)	< 0.001
Age at diagnosis distribution < 40 40 - 60 > 60	38(16.7%) 128 (56.4%) 61 (26.9%)	83 (33.2%) 111 (44.4%) 56 (22.4%)	24 (64.9%) 10 (27.0%) 3 (8.11%)	< 0.001

Gender Male Female	18 (7.7%) 216 (92.3%)	54 (21.3%) 200 (78.7%)	29 (70.7%) 12 (29.3%)	< 0.001
BMI	23.9; 24.6 (±4.2)	24.8; 25.0 (±3.8)	24.2; 24.5 (±3.9)	0.52
Onset as "acute hepatitis"	11 (4.7%)	126 (49.6%)	6 (14.6%)	< 0.001
HBsAg+	0	1 (0.4%)	0	0.67
AntiHBc+	14 (5.6%)	18 (7.1%)	1 (2.4%)	0.55
AntiHCV+	3 (1.3%)	8 (3.2%)	0	0.39
Associated autoimmune conditions	100 (42.7%)	75 (29.5%)	21 (51.2%)	0.002
AST (xUNL)	1.3; 1.8 (±2.6)	8.5; 15.0 (±16.6)	2.2; 4.7 (±11.0)	< 0.001
ALT (xUNL)	1.6; 2.3 (±3.1)	11.6; 18.4 (±18.5)	2.2; 6.2 (±12.8)	< 0.001
IgG mg/dl	1260; 1113.5 (±751.5)	1884; 1923.5 (±1137.5)	1205; 1039.5 (±817.3)	< 0.001
IgA mg/dl	195.5; 204.7 (±165.2)	250; 288.1 (±239.0)	210; 184.1 (±138.8)	0.03
IgM mg/dl	246; 285.3 (±262.4)	137; 167.9 (±172.6)	103; 124.4 (±113.1)	< 0.001
GGT (xUNL)	3.8; 5.8 (±5.5)	2.8; 3.8 (±3.6)	4.3; 6.1 (±6.6)	< 0.001
Alkaline phosphatase (xUNL)	1.7; 2.2 (±1.6)	1.1; 1.4 (±0.9)	1.5; 2.1 (±1.5)	< 0.001
PPT 10^3/mm^3	241; 248.4 (±72.5)	209; 212.4 (±86.9)	248; 254.1 (±108.2)	< 0.001
Total bilirubin mg/dl	0.7; 1.07 (±1.50)	1.58; 4.2 (±5.6)	1.2; 2.8 (±3.9)	< 0.001
ANA positivity	95 (55.2%)	133 (76.9%)	10 (38.5%)	< 0.001
AMA positivity	129 (76.3%)	5 (2.9%)	0 (0.0%)	< 0.001
SMA positivity	18 (11.2%)	67 (39.6%)	5 (19.2%)	< 0.001
LKM positivity	4 (2.7%)	16 (10.3%)	0 (0.0%)	0.009

Table 3: *Comparison between autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis patient groups at diagnosis (median; mean ± standard deviation for continuous variable; absolute and relative frequencies (%) for categorical variables). AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis*

The PBC and PSC patient groups presented significantly higher mean levels of both GGT and alkaline phosphatase, whereas AIH was characterised by the highest levels of transaminases and, as was to be expected, IgG; high IgM values were associated with PBC (Table 3). Biopsy proven cirrhosis at presentation was diagnosed in 7.6% of patients with AIH, in 22.7% of those with PBC and in 10.7% of those with PSC.

The mean histological stage of PBC at diagnosis was 1.9 ± 0.84, and the Mayo score prognostic index was 3.0 ± 2.08 (data not shown).

Type I AIH was highly predominant (93.7%, n = 238), whereas type II AIH was recorded in only 16 patients. A comparison of the biochemical, serological and histological features between type 1 and type 2 AIH is reported in table 4. The two forms of AIH significantly differed in relation to the age at presentation, with an earlier onset in type II compared with type I AIH (33.5 ± 15.9 vs. 47.6 ±16.2 years, respectively, $p < 0.001$). No other significant clinical or biochemical differences were observed.

Variable	AIH Type I (n=238)	AIH Type II (n=16)	P
Age at diagnosis	48.5; 47.6 (±16.2)	33.5; 33.5 (±15.9)	<0.001
Age at diagnosis distribution ≤20 21-44 ≥45	17 (7.1%) 79 (33.2%) 138 (57.9%)	4 (25%) 8 (50%) 4 (25%)	0.04 0.27 0.02
Gender Male Female	50 (21%) 188 (79%)	4 (25%) 12 (75%)	0.95
BMI	25; 25.2 (±4.2)	24; 24.3 (±4.5)	0.43
Onset as “acute hepatitis”	121 (50.8%)	5 (31.2%)	0.21
HBsAg+	2 (0.8%)	0 (0%)	0.27
AntiHBc+	17 (7.1%)	1 (6.2%)	0.71
AntiHCV+	10 (4.2%)	2 (12.5%)	0.36
Associated autoimmune conditions	67 (28.1%)	8 (50%)	0.12
AST (xUNL)	15.4 (±16.5)	10.3 (±17.5)	0.23
ALT (xUNL)	19.2 (±18.5)	10.6 (±11.1)	0.07
IgG mg/dl	1912.6 (±1161.9)	2105.0 (±620.1)	0.51
IgA mg/dl	295.9 (±358.0)	169.4 (±105.5)	0.16
IgM mg/dl	169.3 (±177.5)	146.6 (±57.4)	0.61
γGT (xUNL)	3.9 (±3.7)	2.4 (±1.7)	0.11
Alkaline phosphatase (xUNL)	1.4 (±0.9)	1.1 (±1.0)	0.32
PLT 10^3/mm^3	213.5 (±84.2)	199.2 (±117.9)	0.58
Total bilirubin mg/dl	4.4 (±5.7)	1.1 (±0.7)	0.02

Table 4: *Comparison between autoimmune hepatitis type I and type II at diagnosis (median; mean ± standard deviation for continuous variable; absolute and relative frequencies (%) for categorical variables).*

AIH: Autoimmune Hepatitis

The AIH/PBC overlap syndrome was recorded in 28 cases, while just 5 cases of the AIH/PSC overlap syndrome were observed. The clinical characteristics of the patients are summarised in table 5. As expected, patients with AIH/PSC overlap were younger than the AIH/PBC patients, and the serum transaminase levels were also higher in the first group compared to AIH/PBC. Both conditions were characterised by positivity for non-organ-specific autoantibodies.

Variable	AIH/PBC overlap (n=28)	AIH/PSC overlap (n=5)	P
Age at diagnosis	50.0 ±14.8	47.6 ±15.0	0.15
Gender Male Female	7 (25.0%) 21 (75.0%)	5 (100%) 0	0.007

BMI	24.5 (±4.3)	23.8 (±1.6)	0.74
Onset as "acute hepatitis"	6 (21.4%)	3 (60.0%)	0.11
HBsAg+	1 (3.6%)	0	1.00
AntiHBc+	3 (10.7%)	0	1.00
AntiHCV+	1 (3.6%)	0	1.00
Associated autoimmune conditions	11 (39.3%)	3 (60.0%)	0.62
AST (xUNL)	3.7; 9.9 (±12.3)	14.4; 11.3 (±8.9)	0.84
ALT (xUNL)	4.9; 12.0 (±14.5)	18.7; 27.4 (±30.2)	0.31
IgG mg/dl	1789; 1730.0 (±756.1)	1545.0; 1545.0 (±247.5)	0.61
IgA mg/dl	236; 243.9 (±123.1)	188.5; 188.5 (±9.2)	0.46
IgM mg/dl	410; 415.7 (±248.4)	158.5; 158.5 (±33.2)	0.11
γGT (xUNL)	5.3; 7.1 (±5.4)	6.3; 7.7 (±3.4)	0.55
Alkaline phosphatase (xUNL)	1.7; 2.3 (±1.9)	2.6; 2.2 (±0.8)	062
PLT 10^3/mm3	260; 226.6 (±102.8)	197.5; 197.5 (±70.0)	0.55
Total bilirubin mg/dl	1.6; 3.5 (±5.8)	1.8; 4.9 (±6.8)	0.79
ANA+	13 (72.2%)	3 (75.0%)	1.00
AMA+	12 (66.7%)	0	0.03
SMA+	5 (27.8%)	2 (50.0%)	0.57
LKM+	1 (5.9%)	0	1.00
p-anca+	0	2 (50.0%)	0.07

Table 5: *Comparison between autoimmune hepatitis/primary biliary cirrhosis overlap and autoimmune hepatitis/primary sclerosing cholangitis overlap syndromes at diagnosis (median; mean ± standard deviation for continuous variable; absolute and relative frequencies (%) for categorical variables).*

AIH: Autoimmune Hepatitis; PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis

Immunosuppressive therapy (steroids, or steroids plus azathioprine combination, or azathioprine as maintenance) was the elective treatment for 157/254 patients with AIH (61.8%). Three patients with AIH were taking mycophenolate mofetil (1.18%), 2 cyclosporine A (0.79%) and 8 UDCA as monotherapies (3.15%); 83 patients (32.6%) were not taking any pharmacological intervention (the majority of them, i.e. 76% were incident cases at the moment of diagnosis). One hundred and seventy-three patients with PBC were taking UDCA (73.9%), 25 of them in combination with an immunosuppressive agent (steroid, azathioprine, MMF, FK506 or cyclosporine A); 61 patients with PBC were untreated. Thirty-two patients were taking UDCA (78%), 11 of whom were taking it in combination with an immunosuppressant agent. Concerning patients with PSC, 9 (21.25%) were untreated, 21 were taking UDCA as a monotherapy (51.22%) and 11 were taking UDCA plus immunosuppressant agents (prednisone, azathioprine, cyclosporine or MMF).

Discussion

The present nationwide study illustrates the clinical characteristics of a population of patients with autoimmune liver diseases in 2010. Although the lack of data from some referral centres limits the generalisation of our results, it provides original recent information about the profile of autoimmune diseases in Italy; in fact, the study population is quite uniformly distributed between Northern, Central and Southern Italy.

The cohort of patients with AIH is the most representative of our study in terms of the sample size selected from the Italian population. The clinical picture of AIH patients highlights some of the characteristics belonging to the classical AIH phenotype; moreover, as expected, high levels of transaminases and hypergammaglobulinaemia provide the most important biochemical marker of the disease. Nevertheless, the data reveal some other points of particular interest. The first point regards the high prevalence of acute disease onset, present in the 49.6% of the patient population. This prevalence is in line with that previously reported in the "Bologna experience" (40%) [22]. A high incidence of acute onset has also been reported in Alaska natives (34.7%) [5]. Although no formal definition of acute onset exists, this condition is generally identified by the presence of jaundice, high level of transaminases (usually >10-fold the upper normal limits) and compromised liver function (INR>1.5) [23]. The high prevalence of early onset revealed in the present study may be biased by the fact that most of the participating centres are tertiary referral centres, thus the patients described in this study probably represent those with more active disease states. Nevertheless, this high prevalence suggests that AIH should no longer be deemed a chronic asymptomatic disease, but that it should be considered in the differential diagnosis of acute hepatitis in the absence of a definite aetiology. The presence of cirrhosis was noticed in 7.6% of patients at the time of diagnosis; this percentage is lower than that reported in other nationwide studies of AIH [4,6,9,10] and is only comparable to that reported for Japan (6.4%) [8] and for the Netherlands (12%) [11]. This observation can be explained by i) the relatively recent survey period of the present study (i.e. 2010), whereas in most other nationwide studies the enrolment period started before the 1990's (refs), and ii) by the high prevalence of acute onset that indicates short disease duration. Another interesting point arises from the comparison of the epidemiological, clinical and biochemical features between type 1 and 2 AIH. To the best of our knowledge, this is the largest series of adult patients with type 2 AIH ever published. Only one paper published in 1992 [24] reported that LKM1 was rarely found in patients with chronic hepatitis, but the number of patients studied in that case was too small to allow any clinical evaluations. Our series of patients with type 2 AIH, although significantly smaller than that with type one, suggests that the two subgroups are almost identical in terms of ...; the only major difference is the trend toward lower age of onset in type 2. Based on these observations, we believe that a sub-classification of AIH into the classical subgroups has no clinical grounds, maintaining only a historical serological significance.

Anti-HCV positivity was associated in 3.2% of cases. The overall prevalence of anti-HCV positivity is similar to that of the general population in Italy [25], thus it is not surprising that some cases of AIH/HCV overlap are identified considering the high background prevalence of HCV in Italy. In such cases, the diagnosis of AIH may be overlooked and AIH could remain untreated. It is thus extremely important that a careful evaluation of the clinical phenotype and of the liver biopsy is performed such that the existence of a double mechanism of liver damage is not overlooked.

At present, PBC and AIH are the most important forms of autoimmune liver disease in Italy, whereas PSC still constitutes a rare disease. Obviously, epidemiological findings cannot be drawn from our survey, but the data do provide us with a general impression suggesting that the incidence of AIH may be increasing in Italy. PBC is diagnosed around menopause in roughly 50% of cases, and has an onset after 60 years of age in 26.9% of cases. In the Newcastle PBC database, which includes 1023 patients, 397 cases (39%) were over the age of 65 at the moment of presentation [26]. Moreover, PBC is diagnosed at an early histological stage, presenting an important clinical problem. Indeed, we propose that the methods used to identify clinical cases are reviewed and the referral bias to the tertiary centres reconsidered as well as the referral bias to the tertiary centres. Nevertheless, over recent years, increasing numbers of asymptomatic cases of PBC have been diagnosed, where the suspicion for the diagnosis mainly arises from altered liver function tests [27].

Conclusion

In conclusion, the results of this national survey addressing the prevalence and incidence of autoimmune liver disease in the year 2010, although limited to just a few Italian centres (n = 15), indicate that this condition should no longer be considered as rare diseases. In particular, the results reveal the highest ever reported prevalence and incidence of AIH for Italy. The clinical characteristics are comparable with those detected in other countries. Further studies are warranted to prospectively investigate the natural history of the disease and the optimisation for treatment therapies.

Acknowledgements: No support in the form of grants, equipment, drugs were received for the survey.

Bibliography

1. Mieli Vergani G and Vergani D. "Autoimmune hepatitis". *Nature Reviews Gastroenterology and Hepatology* 8.6 (2011): 320-329.

2. Al-Chalabi T., *et al*. "Impact of gender on the long-term outcome and survival of patients with autoimmune hepatitis". *Journal of Hepatology* 48.1 (2008): 140-147.

3. Strassburg CP and Manns MP. "Therapy of autoimmune hepatitis". *Best Practice and Research Clinical Gastroenterology* 25.6 (2011): 673-687.

4. Boberg KM., *et al*. "Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population". *Scandinavian Journal of Gastroenterology* 33.1 (1998): 99-103.

5. Hurlburt KJ., *et al*. "Prevalence of autoimmune liver disease in Alaska natives". *American Journal of Gastroenterology* 97.9 (2002): 2402-2407.

6. Werner M., *et al*. "Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study". *Scandinavian Journal of Gastroenterology* 43.10 (2008): 1232-1240.

7. Ngu JH., *et al*. "Population-based epidemiology study of autoimmune hepatitis: a disease of older women?" *Journal of Gastroenterology and Hepatology* 25.10 (2010): 1681-1686.

8. Abe M., *et al*. "Present status of autoimmune hepatitis in Japan: a nationwide survey". *Journal of Gastroenterology* 46.9 (2011): 1136-1141.

9. Kim BH., *et al*. "Clinical features of autoimmune hepatitis and comparison of two diagnostic criteria in Korea: a nationwide, multicenter study". *Journal of Gastroenterology and Hepatology* 28.1 (2013): 128-134.

10. Gronbaeck L., *et al*. "Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study". *Journal of Hepatology* 60.3 (2014): 612-617.

11. Van Gerven NM., *et al*. "Epidemiology and clinical characteristics of autoimmune hepatitis in the Netherlands". *Scandinavian Journal of Gastroenterology* 49.10 (2014): 1245-1254.

12. Bowlus CL and Gershwin ME. "The diagnosis of primary biliary cirrhosis". *Autoimmunity Reviews* 13 (2014): 441-444.

13. Podda M., *et al*. "The limitation and hidden gems of the epidemiology of primary biliary cirrhosis". *Journal of Autoimmunity* 46 (2013): 81-87.

14. Sagnelli E., *et al*. "The importance of HCV on the burden of chronic liver disease in Italy: a multicenter prevalence study on 9,997 cases". *Journal of Medical Virology* 75.4 (2005): 522-527.

15. Hirschfield GM., *et al*. "Primary sclerosing cholangitis". *Lancet* 382.9904 (2013): 1587-1589.

16. Lindkvis B., *et al.* "Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden". *Hepatology* 52.2 (2010): 571-577.

17. Molodecky NA., *et al.* "Incidence of primary sclerosing cholangitis: a systematic review". *Hepatology* 53.5 (2011): 1590-1599.

18. Boonstra K., *et al*. "Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review". *Journal of Hepatology* 56.5 (2012): 1181-1188.

19. Scheuer PJ. "Primary biliary cirrhosis". *Proceedings of the Royal Society of Medicine* 60.12 (1967): 1257-1260.

20. Chazouillères O., *et al*. "Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy". *Hepatology* 28.2 (1998): 296-301.

21. Hennes EM., *et al*. "Simplified criteria for the diagnosis of autoimmune hepatitis". *Hepatology* 48.1 (2008): 169-176.

22. Muratori P., *et al*. "Autoimmune hepatitis in Italy: The Bologna experience". *Journal of Hepatology* 50.6 (2009): 1210-1218.

23. Yamamoto K., *et al*. "Intractable Liver and Biliary Diseases Study Group of Japan. Prognosis of autoimmune hepatitis showing acute presentation". *Hepatology Research* 43.6 (2013): 630-638.

24. Czaja AJ., *et al*. "Frequency and significance of antibodies to liver/kidney microsome type 1 in adults with chronic active hepatitis". *Gastroenterology* 103.4 (1992): 1290-1295.

25. Bellentani S., *et al*. "Clinical course and risks factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study". *Gut* 44.6 (1999): 874-880.

26. Newton JL., *et al*. "Presentation and mortality of primary biliary cirrhosis in older patients". *Age Ageing* 29.4 (2000): 305-309.

27. Floreani A., *et al*. "A 35-year follow-up in a large cohort of patients with primary biliary cirrhosis seen at a single centre". *Liver International* 31.3 (2011): 361-368.

Volume 1 Issue 4 November 2016